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Differential multiple sclerosis treatment allocation between Australia and New Zealand associated with clinical outcomes but not mood or quality of life

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ABSTRACT

Background: Differential treatment allocation may impact on clinical phenotype in MS and in turn upon quality of life (QoL).
Objectives: (a) Investigate the association between disease-modifying drugs (DMDs) use and relapse frequency, disability, clinically significant fatigue, and physical and mental health-related QoL among participants with MS residing in Australia and New Zealand (NZ); (b) assess whether these associations differed between Australia and NZ.
Methods: Disability and fatigue were measured by PDDS and FSS, respectively. QoL was assessed by MSQOL-54. Associations were assessed by binomial and multinomial logistic regression, as appropriate. Multivariable models were adjusted for demographic and clinical covariates, as appropriate.
Results: 837 participants (627 from Australia; 210 from NZ) were identified from an online cohort of people with MS. First- and second-generation DMD use was associated with higher adjusted-odds of fatigue and disability, though not with 12-month relapse number. DMD use was not independently associated with physical or mental QoL. The association of first-generation DMD use with moderate disability differed between nations, such that treatment was associated with lower odds in Australia but not in NZ; a similar but a small difference was found for severe disability. No differences were seen in the DMD association with relapse number, nor with fatigue or QoL, between Australia and NZ.
Conclusion: The differential treatment allocation associations in NZ are evident in the DMD-disability association, but there is no evidence that this treatment regimen has negative associations with fatigue, mood, or QoL.

1. Introduction

Multiple sclerosis (MS) is an incurable, lifelong inflammatory disease of the central nervous system associated with axon degeneration and demyelination in the brain and spinal cord.(Compston et al., 2005) Disease-modifying drugs (DMDs) have been demonstrated to reduce the frequency and severity of clinical attacks or relapses, and there are emerging data indicating that they may limit the accumulation of disability.(Lizak et al., 2017; Tur et al., 2018; Vargas and Tyor, 2017; Vidal-Jordana, 2018) The side effects of these medications, which can vary by DMD, frequently render them intolerable for people living with MS.(Broadley et al., 2014; Subei and Ontaneda, 2015; Vargas and Tyor, 2017; Winkelmann et al., 2016) Moreover, though ocrelizumab has now been demonstrated to have efficacy in primary progressive MS, this

Abbreviations: DMD, disease modifying drug; EDSS, expanded disability status scale; FSS, fatigue severity scale; HOLISM, health outcomes and lifestyle interventions in a sample of people with multiple sclerosis; MS, multiple sclerosis; NZ, New Zealand; PDDS, patient-determined disease steps; PHARMAC, pharmaceutical management agency; QoL, quality of life

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is the only such drug available for people with progressive MS types. The more recently released second-generation DMDs have advantages in terms of ease of administration and efficacy when compared with drugs such as the interferons, but nonetheless have side effect profiles of concern.(Vargas and Tyor, 2017)

Of particular interest here, there are regional differences in the availability of these DMDs. For example, first and some second generation DMDs were listed for use in MS by the Pharmaceutical Benefits Advisory Committee in Australia in 2012, but only first generation DMDs were listed for use in MS in New Zealand (NZ) by the Pharmaceutical Management Agency (PHARMAC) at that time, though second-generation DMDs have become available since. This situation creates a natural setup where treatment exposures vary between two otherwise quite similar regions, both in terms of population, medical infrastructure, and other characteristics.(Taylor et al., 2010; Taylor et al., 2013) In this fashion, we can assess the relationship of DMD use with various clinical outcomes in MS and whether these relationships differ between nations. It is not unreasonable to expect some such differences to be evident—the requirements for prescribing DMDs in MS are much stricter in NZ, in terms of disability level and relapse number in the previous 1–2 years, these independently assessed by committee, and there are stopping criteria to discontinue therapy in those where progression occurs despite treatment.(Pharmaceutical Management Agency, 2012, 2014). In Australia, on the other hand, public subsidy of MS medications is much more at the discretion of the treating physician, essentially only requiring diagnosed MS and having had two diagnosed relapses in the preceding two years(Department of Health and Ageing, 2012). What is uncertain is whether this differential treatment allocation impacts negatively on other elements of clinical course, particularly fatigue or patient quality of life (QoL).

While DMDs have been demonstrated to impact on disability and relapse, other aspects of clinical course, including fatigue, and quality of life, can only be treated indirectly via immunomodulation of clinical course, if at all. Of these, fatigue is one of the most prevalent and debilitating complications,(Johnson, 2008; Nagaraj et al., 2013) affecting up to 80% of people living with MS. Health-related QoL in people with MS is often significantly lower than comparator populations, and likewise correlates strongly with clinical severity and disease course. (Janardhan and Bakshi, 2002; Pittion-Vouyovitch et al., 2006; Wynia et al., 2008) Since fatigue, mood, and QoL are strongly impacted by relapse and disability in MS,(Amato et al., 2001; Janardhan and Bakshi, 2002) the differential allocation of DMDs could potentially have a negative impact on QoL, both directly due to untreated MS symptoms and vicariously via impacts of MS on lifestyle and independent living.

In this study of people living with MS in Australia and NZ, we aimed to (1) investigate the association between DMD use and clinical outcomes among people living with MS residing in Australia and NZ; (2) assess whether these associations differed significantly between Australia and NZ.

2. Materials and methods

2.1. Participants and recruitment

The participants of this study were from the international HOLISM (Health Outcomes and Lifestyle in a Sample of people with Multiple Sclerosis) study in 2012 (Hadgkiss et al., 2013). The aim was to explore the relationship of current lifestyle with clinical outcomes and quality of life among people living with MS. The methodology of this study has been described previously, but briefly, participants were recruited via online forums and related venues to participate in an online survey of the demographic, clinical and lifestyle characteristics of people living with confirmed MS. Participants were included in the HOLISM baseline study if they had doctor-diagnosed MS and were aged ≥18 years. The HOLISM study was approved by St Vincent's Hospital Melbourne Human Research Ethics Committee (LRR 055/12) and The University of Melbourne Health Sciences Human Ethics Sub-Committee (Ethics ID: 1545102). The present analysis is circumscribed to include only participants who reported residing in Australia or New Zealand at the time of survey completion.

2.2. Data collection and tools used

2.2.1. DMD use

We presented survey participants with a list of MS-specific disease-modifying therapies, including immunomodulatory and symptom-ameliorating medications then available internationally. However, given the focus of the present analysis on Australia and NZ, we will constrain DMDs to the medications then available in these nations. Thus, we classified first generation DMDs to include interferon-β and glatiramer acetate medications, and second generation DMDs to include fingolimod, cladribine, and natalizumab. DMD use was classified into three groups: (a) no DMD use; (b) first-generation DMD use only; and (c) second-generation DMD use, with or without first-generation DMD use.

2.2.2. Clinical outcomes

Relapse number in the preceding year was queried, including the overall number and those diagnosed as valid relapses by a medical practitioner; only the latter are included here. For analyses, we categorised relapse number into three groups: (a) no relapse in the preceding year, (b) 1 relapse in the preceding year, (c) ≥2 relapses in the preceding year. Disability was assessed using the Patient-Determined Disease Steps (PDDS) scale,(Hohol et al., 1995) which has been validated against the Expanded Disability Status Scale (EDSS). A PDDS score of 1–3 was indicative of mild disability, 4–6 indicative of gait disability (moderate disability), and 7–8 indicative of severe mobility disability (severe disability). Fatigue was assessed using the Fatigue Severity Scale (FSS),(Krupp et al., 1989) a mean score ≥4 indicative of clinically significant fatigue. Depression risk was assessed using the Patient Health Questionnaire-2, a score of 3 or more indicating a positive depression screen.(Lowe et al., 2005) Quality of life was assessed using the MSQOL-54, which estimates two core subdomains of physical QoL and mental QoL (Vickrey, 1995).

2.2.3. Other lifestyle factors

Participants were queried as to their current smoking status (never/former/current). Alcohol intake was queried, both frequency and typical number of standard drinks per sitting, this used to estimate an alcohol load which we categorised as (a) high: > 30g /day for females and > 45g /day for males; (b) moderate: up to 30g /day for females and up to 45g /day for males; (c) low: < 15g / week.(Liang et al., 2012) We assessed physical activity using the short form of the International Physical Activity Questionnaire (IPAQ-SF) (Craig et al., 2003), the resulting metabolic equivalent of task (MET) minutes categorising participants into high-active (vigorous-intensity active on at least 3 days, or 7 days of walking, or moderate or vigorous activity), moderate-active (3 or more days of vigorous activity of at least 20 minutes per day, or 5 or more days of moderate or higher intensity activity or walking of at least 30 minutes per day) and low-active (less active than the moderate category). We also queried whether participants took vitamin D and/or omega-3 supplements, as well as the type and dose thereof. Antidepressant and anxiolytic prescription medication use was also queried. We assessed diet quality using the Diet Habits Questionnaire (DHQ), modified slightly to remove redundant questions on alcohol and also questions on salt intake, as described previously.(Hadgkiss et al., 2015) Total DHQ score ranged from 20 to 100, a score of 100 indicating the healthiest dietary habits. Finally, we queried participants' meditation frequency, categorised as never, less than once per week, 1–4 times per week, and ≥5 times per week.

2.3. Data analysis

The characteristics of the cohort were summarised using mean (standard deviation) and number (percentage) for continuous and categorical variables respectively.

Association of DMD use and country with categorised relapses (1 relapse vs no relapse; 2 or more relapses vs no relapse), disability (moderate vs mild; severe vs mild), clinically significant fatigue, positive depression screen, and physical and mental QoL was explored using binomial or multinomial logistic regression (for categorical outcomes) and linear regression (for continuous outcomes). Models were adjusted for age, sex, MS type, disability, fatigue, ongoing relapse symptoms, and antidepressant medication use, as appropriate. Analyses were constrained to where data were available for all model covariates (complete case analysis).

Interactions were used to assess whether associations of DMD differed between Australia and NZ. Stratum-specific associations of DMD with outcomes are presented for Australia and NZ.

Given as our primary analyses were based on an a priori hypothesis that treatment associations with clinical outcomes would differ by country, results are not adjusted for multiple comparisons.

All analyses were performed using STATA/SE, version 15.1 (StataCorp, College Station, USA).

4. Results

4.1. Cohort characteristics

A total of 837 people living with MS in in Australia and NZ, of which 627 (74.9%) were from Australia and 210 (25.1%) from NZ. Half (50.3%) of respondents took first generation DMDs, while 15.8% were using second-generation DMDs. As would be expected from the differential treatment regimes, a larger proportion of participants in NZ than Australia were not using any DMDs (60.1% vs 25.0%); more similar proportions were using first-generation DMDs in NZ and Australia (37.4% vs 54.7%), but the proportion using second-generation DMDs was much smaller in NZ than Australia (2.5% vs 20.3%, p value $<$ 0.001).

The majority of respondents were female (81.6%), and of mean age 47.1 years (SD: 10.8). A majority (60.1%) of participants had mild disability (PDDS 1–3), while roughly one-third had moderate disability and 7.6% had severe disability. Nearly half of participants had had at least one relapse in the preceding year, half of these having had two or more. Sixty-two percent of respondents had clinically significant fatigue. The mean physical and mental QoL were 64.1 (SD: 20.1) and 70.9 (SD: 19.8), respectively. Other cohort characteristics can be found in Table 1.

4.2. Relapse number in the preceding year

Relapse number in the preceding year was not significantly associated with DMD use, though on adjustment for age, sex and MS type, first-generation DMD use was associated with a significantly lower odds of having had 1 relapse in the preceding year ($p = 0.035$); a similar association with 2+ relapses in the preceding year did not reach significance ($p = 0.33$) (Table 2). The odds of having 1 or 2+ relapses in the preceding year did not vary between Australia and NZ.

4.3. Disability

As in Table 3, the odds of having moderate or severe disability did not significantly vary by DMD medication use. However, on controlling for age, sex, MS type and whether participants had ongoing symptoms from a recent relapse, the odds of having moderate disability were higher among those on first-generation ($p = 0.089$) and second-generation ($p = 0.001$) DMDs, this change due largely to the impact of adjusting for age. Second-generation DMD use was associated with an even stronger association with severe disability ($p = 0.001$), though first-generation DMD use was not associated ($p = 0.56$). The odds of moderate disability were significantly greater among NZ participants ($p < 0.001$), persisting on adjustment, though no significant difference between nations was seen for severe disability. Further adjustment for lifestyle factors did not attenuate these associations (data not shown).

4.4. Clinically significant fatigue

The odds of clinically significant fatigue, as defined by FSS ≥ 4, was significantly higher among those on second-generation ($p = 0.015$) DMDs, persisting on adjustment for age, sex, MS type, disability level, and whether participants were experiencing ongoing symptoms from a recent relapse. A similar association was seen for first-generation DMDs ($p = 0.057$), becoming significant on adjustment ($p = 0.016$; Table 4). No differences in clinically significant fatigue were seen between Australia and NZ. No associations materially differed on further adjustment for lifestyle factors (data not shown).

4.5. Depression screen

The odds of positive depression screen, as measured by a PHQ-2 score > 2, while not significantly different among those using first-generation DMDs, were two-fold higher among those using second-generation DMDs, though this association attenuated and became nonsignificant on adjustment for age, sex, MS type, disability level, fatigue, and antidepressant medication use (Table 5). While depression risk did not significantly differ between Australia and NZ in univariable models, on adjustment for demographics and clinical features, the odds of depression was significantly lower among NZ participants ($p = 0.032$).

4.6. Physical and mental health-related quality of life

As in Table 6, first-generation DMD use was not significantly associated with physical nor mental QoL, either alone or on adjustment for age, sex, MS type, disability level, clinically significant fatigue, and whether participants were experiencing ongoing symptoms from a recent relapse. Second-generation DMD use, however, was associated with significantly lower physical ($p = 0.007$) and mental ($p = 0.007$) QoL, the association with physical QoL persisting on adjustment, while that with mental QoL attenuated and became nonsignificant. Interestingly, while neither physical nor mental QoL scores significantly differed between Australian and NZ participants, on controlling for demographic and clinical covariates, NZ participants had a significantly higher physical QoL ($p = 0.004$); similarly, higher mental QoL among NZ participants did not reach significance ($p = 0.13$).

4.7. Differences in DMD-outcome associations between Australia and NZ

In assessing differences in the associations of DMD and outcomes between nations (Table 7), no significant differences were seen in the associations with relapse number in the preceding year, as seen in the aggregate. First-generation DMD use was associated with a significantly higher frequency of moderate disability in NZ ($p = 0.001$), as in all persons, while no significant association was seen in Australian participants ($p = 0.072$), this difference significant ($p_{interaction} = 0.036$). An analogous trend was seen for severe disability – first-generation DMD being associated with greater disability risk in NZ but not Australia, though this interaction did not reach significance ($p_{interaction} = 0.14$). There was no statistical difference in the associations of second-generation DMDs and moderate disability between nations ($p_{interaction} = 0.49$), though the small numbers precluded quantitative assessment of this interaction for severe disability. The association of first-generation DMD use with clinically significant fatigue was not

Table 1
Cohort characteristics, overall and by country.

	Australia *n/N* (%)	New Zealand *n/N* (%)	Total *n/N* (%)	*P* value
Sex				
Male	103/587 (17.6%)	42/200 (21.0%)	145/787 (18.4%)	
Female	484/587 (82.5%)	158/200 (79.0%)	642/787 (81.6%)	0.28
Age, years (mean (SD))	46.7 (10.8)	48.3 (10.8)	47.1 (10.8)	0.063
Smoking status				
Never	304/589 (51.6%)	93/198 (47.0%)	397/787 (50.4%)	
Former smoker	238/589 (40.4%)	87/198 (43.9%)	325/787 (41.3%)	
Current smoker	47/589 (8.0%)	18/198 (9.1%)	65/787 (8.3%)	0.52
Alcohol consumption*				
Low	344/587 (58.6%)	94/197 (47.7%)	438/784 (55.9%)	
Moderate	236/587 (40.2%)	102/197 (51.8%)	338/784 (43.1%)	
High	7/587 (1.2%)	1/197 (0.5%)	8/784 (1.0%)	**0.015**
Physical activity				
Low active	226/583 (38.8%)	78/196 (39.8%)	304/779 (39.0%)	
Moderate active	185/583 (31.7%)	68/196 (34.7%)	253/779 (32.5%)	
High active	172/583 (29.5%)	50/196 (25.5%)	222/779 (28.5%)	0.53
Vitamin D supplementation *				
None	81/572 (14.2%)	14/182 (7.7%)	95/754 (12.6%)	
1–2000 IU	156/572 (27.3%)	53/182 (29.1%)	209/754 (27.7%)	
2001–5000 IU	213/572 (37.2%)	62/182 (34.1%)	275/754 (36.5%)	
> 5000 IU	122/572 (21.3%)	53/182 (29.1%)	175/754 (23.2%)	**0.033**
Meditation frequency				
Never	207/585 (35.4%)	86/197 (43.7%)	293/782 (37.5%)	
Less than once per week	166/585 (28.4%)	47/197 (23.9%)	213/782 (27.2%)	
1 – 4 times per week	148/585 (25.3%)	46/197 (23.4%)	194/782 (24.8%)	
5 or more times per week	64/585 (10.9%)	18/197 (9.1%)	82/782 (10.5%)	0.21
Physical health-related quality of life (mean (SD))	64.0 (20.5)	64.6 (19.0)	64.1 (20.1)	0.74
Mental health-related quality of life (mean (SD))	70.4 (20.2)	72.2 (18.5)	70.9 (19.8)	0.30
DMD use*				
None	148/591 (25.0%)	121/198 (60.1%)	267/789 (33.8%)	
First-generation	323/591 (54.7%)	74/198 (37.4%)	397/789 (50.3%)	
Second-generation	120/591 (20.3%)	5/198 (2.5%)	125/789 (15.8%)	< **0.0-01**

Results in boldface denote statistical significance ($p < 0.05$).
Note: Differences in denominators in cells reflect missing data for specified parameters.
* Significance of differences of dichotomous and polytomous variables between Australia and NZ assessed by Chi-square tests. Differences of continuous variables between Australia and NZ assessed by *t* test.

materially different between Australia and NZ ($p_{interaction} = 0.29$); small sample size precluded examination of inter-nation differences in the association of second-generation DMDs and fatigue. Neither first nor second-generation DMD use was significantly associated with positive depression screen in either Australia or NZ participants, and accordingly no significant differences were seen between nations. Similarly, there was no evidence of difference in the associations of DMDs and physical or mental quality of life in Australia or NZ, and likewise no significant differences between nations were evident.

Results evaluating treatment duration showed generally similar results: in Australia, longer DMD treatment durations were associated with lower risks of having more relapses and moderate disability, while in NZ there was a trend towards a greater risk of having more relapses and of moderate and severe disability, the differences for disability evident ($p_{interaction} = 0.009$ for moderate, $p_{interaction} = 0.082$ for severe). Of note, second-generation DMD use, while not associated with relapse number, was associated with greater risk of moderate and severe disability in Australia (NZ could not be quantitatively evaluated due to small cell sizes). Alongside the inverse associations seen between first-generation DMDs and disability, this may reflect treatment switching from first to second-generation DMDs in Australia. No associations between DMD treatment duration and fatigue or disability were evident in either Australia or NZ. Importantly, and in agreement with the results seen for overall DMD usage, no significant differences in the associations of first and second-generation DMD treatment duration and physical ($p_{interaction} = 0.47$, $p_{interaction} = = 0.65$) and mental QoL ($p_{interaction} = 0.73$, $p_{interaction} = 0.39$) were evident between nations.

5. Discussion

Here, we have endeavoured to use the differential allocation of DMD therapies in MS between Australia and New Zealand to assess whether a more restricted allocation of DMDs in NZ impacted negatively on fatigue and quality of life. We found that, while the association of DMDs with disability significantly differed between the two nations, as expected given the different allocation regimes, there was no evident impact on either fatigue, depression, or quality of life.

Australia and New Zealand share a similar geographic location and a commonality of government and healthcare systems. Both have universal access to care for citizens and permanent residents, and thus, there is not as much of a socioeconomic divide of healthcare access of the sort seen in nations without national health insurance schema. However, differences exist in treatment allocation between Australia and NZ. NZ's smaller economy than that of Australia means that their triage of medical infrastructure has more stringent criteria to be met before treatment can be paid for by the state, and likewise criteria in which treatment will be discontinued where it is not impacting on disease.(Dew and Davis, 2014; Grocott et al., 2013; Taylor and Wonder, 2015; Wonder and Milne, 2011) These criteria are almost wholly absent in Australia where medical practitioners may prescribe pharmaceuticals which are then costed in some part to Medicare. The concern here is not to impugn the rationality of NZ's treatment allocation regime. Indeed, while it is a topic of lively debate,(McNaughton et al., 2006; Taylor and Wonder, 2015) others have shown that the allocation rationales of PHARMAC are sound.(Evans et al., 2016; Grocott et al., 2013) Rather the aim here was to examine whether it has follow-on negative impacts

Table 2
Univariable and adjusted OR of characteristics of relapse number in the preceding year.

	No relapse (%)	One relapse (%)	Two or more relapses (%)	1 relapse vs no relapse Univariable OR (95% CI)	Adjusted OR * (95% CI)	2 or more relapses vs no relapse Univariable OR (95% CI)	Adjusted OR * (95% CI)
DMD use*							
None	134/245 (54.7%)	61/245 (24.9%)	50/245 (20.4%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
First-generation	204/383 (53.3%)	89/383 (23.2%)	90/383 (23.5%)	1.07 (0.72, 1.61)	**0.61 (0.39, 0.97)**	1.18 (0.79, 1.77)	0.79 (0.50, 1.26)
				$p = 0.73$	$p = \mathbf{0.035}$	$p = 0.42$	$p = 0.33$
Second-generation	60/122 (49.2%)	34/122 (27.9%)	28/122 (23.0%)	1.34 (0.79, 2.27)	0.75 (0.42, 1.34)	1.25 (0.72, 2.18)	0.73 (0.39, 1.34)
				$p = 0.29$	$p = 0.33$	$p = 0.43$	$p = 0.31$
Country							
Australia	310/586 (52.9%)	149/586 (25.4%)	127/586 (21.7%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
New Zealand	99/192 (51.6%)	44/192 (22.9%)	49/192 (25.5%)	0.92 (0.62, 1.39)	0.98 (0.63, 1.52)	1.21 (0.81, 1.80)	1.39 (0.90, 2.13)
				$p = 0.71$	$p = 0.93$	$p = 0.35$	$p = 0.14$

DMD multivariable model consisted of 716 observations; country multivariable model consisted on 776 observations (complete case analysis).
Note: Univariable results restricted to complete case analysis did not materially affect any results (data not shown).
* Multinomial logistic regression after adjusting for age, sex, and MS type.

on quality of life and clinical features for people living with MS most directly impacting on QoL, namely fatigue.

Given the PHARMAC guidelines in NZ require minimum relapse rates in the preceding year and minimum levels of disability, (Pharmaceutical Management Agency, 2014) we expected to find significant differences in the DMD associations with these outcomes when comparing Australia and NZ. For disability, we showed precisely this, with disability significantly more common among users of first-generation DMDs in NZ, while no association was seen in Australia. Second-generation DMDs did not differ at all between nations but this may reflect the smaller numbers on these treatments compared to the more commonly used interferon and glatiramer acetate medications. At the same time, however, we did not show any association between DMDs and relapse number, nor a difference in that association between Australia and NZ. This may reflect the self-reported nature of relapses, participants having been queried on the number of doctor-diagnosed relapses in the preceding year. This method is inherently subject to recall bias, as well as inter-patient variability in reporting relapse symptoms to medical practitioners. Also, since our measure of relapse number was only in the year preceding the survey, it may be that patients established on therapy would not show a difference in the DMD-relapse association, even despite differential inclusion criteria.

Of relevance to our study's aims, we found that both first and second-generation DMDs were associated with a greater frequency of clinically significant fatigue, but this association did not differ between Australia and NZ. Importantly, we found no evidence of differences in the association of DMD use with depression between Australia and NZ, nor any difference in the association of DMDs with physical or mental QoL, suggesting that the differential treatment allocation regime in NZ does not adversely impact on mental health or quality of life, despite restricting use to those with more active disease.

5.1. Strengths and limitations

This is the largest study examining DMD use and its associations with clinical outcomes in the Australasian setting. The mode of recruitment, however, may have led to a healthier and self-selected sample which may not fully represent the broader population of people living with MS. The demographic and disease characteristics of the sample are fairly comparable to other studies of MS, however, so while our cohort is healthier, it is nonetheless useable for this purpose. The self-reporting of various outcomes rather than objective measures in clinic is a limitation, since subjectivity necessarily affects one's perceptions and thus, their reporting of disability, fatigue and QoL-related parameters. However, all these measures have been validated against corresponding clinical measures. One feature which would have been of especial use in this analysis is information about the dose and consistency of use of first and second-generation DMDs over time, as well as the degree of adherence to the specified treatment, which would have enabled us to better evaluate the internal consistency and dose-dependency of associations with outcomes, as well as to undertake sensitivity analyses constrained to those with more consistent medication use. While the analyses described here were based on a priori hypotheses, the number of tests – 42 – does mean there is some potential for type-1 error. However, the fact that our main conclusions derive from the absence of significant differences in the DMD-outcome associations between Australia and NZ, this is less of a concern than would be the case if we had drawn conclusions based on significant results. Finally, it is worth noting that the small numbers of patients on DMDs in NZ, particularly the second-generation DMDs, does limit the ability to quantitatively assess the DMD-outcome associations, so replication in other studies would be key. Further to this, the natural experiment of Australia and NZ used in this paper will be used for a similar purpose to examine disability progression, among other outcomes, in the CompANZ Study being conducted presently (Claflin et al., 2018). This study will compare clinical outcomes, mood and QoL between Australian and NZ participants with relapsing-remitting MS. It will

Table 3
Univariable and adjusted OR of characteristics of disability level (PDDS).

				Gait/cane (moderate) disability vs normal/mild disability		Major mobility support (severe) vs normal/mild disability	
	Normal/Mild disability (%)	Gait/Cane (moderate) disability (%)	Major mobility support (severe) (%)	Univariable OR (95% CI)	Adjusted OR * (95% CI)	Univariable OR (95% CI)	Adjusted OR * (95% CI)
DMD use*							
None	151/266 (56.8%)	92/266 (34.6%)	23/266 (8.7%)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
First-generation	254/395 (64.3%)	117/395 (29.6%)	24/395 (6.1%)	0.76 (0.54, 1.06) $p = 0.11$	1.50 (0.94, 2.39) $p = 0.089$	0.62 (0.34, 1.14) $p = 0.12$	1.29 (0.55, 2.99) $p = 0.56$
Second-generation	67/125 (53.6%)	45/125 (36.0%)	13/125 (10.4%)	1.10 (0.70, 1.74) $p = 0.68$	**2.69 (1.48, 4.88)** $p = \mathbf{0.001}$	1.27 (0.61, 2.67) $p = 0.52$	**5.22 (1.92, 14.22)** $p = \mathbf{0.001}$
Country							
Australia	377/593 (63.6)	172/593 (29.0)	44/593 (7.4)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
New Zealand	100/201 (49.8)	85/201 (42.3)	16/201 (8.0)	**1.86 (1.33, 2.62)** $\boldsymbol{p < 0.001}$	**1.70 (1.13, 2.57)** $\boldsymbol{p = 0.011}$	1.37 (0.74, 2.53) $p = 0.31$	1.00 (0.47, 2.14) $p = 0.99$

Results in boldface denote statistical significance ($p < 0.05$).
DMD multivariable model consisted of 758 observations; country multivariable models consisted of 758 observations (complete case analysis).
Note: Univariable results restricted to complete case analysis did not materially affect any results (data not shown).
* Multinomial logistic regression after adjusting for age, sex, MS type, and whether participant was experiencing ongoing symptoms from a relapse in the previous 30 days.

Table 4
Univariable and adjusted OR of characteristics of clinically significant fatigue.

	Clinically significant fatigue (%)	Univariable OR (95% CI)	Adjusted OR * (95% CI)
DMD use*			
None	141/250 (56.4%)	1.00 [Reference]	1.00 [Reference]
First-generation	245/383 (64.0%)	1.37 (0.99, 1.90) $p = 0.057$	**1.64 (1.10, 2.44)** $p = \mathbf{0.016}$
Second-generation	81/116 (69.8%)	**1.79 (1.12, 2.86)** $\boldsymbol{p = 0.015}$	**1.81 (1.04, 3.15)** $\boldsymbol{p = 0.036}$
Country			
Australia	346/558 (62.0%)	1.00 [Reference]	1.00 [Reference]
New Zealand	121/191 (63.4%)	1.06 (0.75, 1.49) $p = 0.74$	0.83 (0.56, 1.23) $p = 0.36$

Results in boldface denote statistical significance ($p < 0.05$).
Multivariable models consisted of 713 observations (complete case analysis).
Note: Univariable results restricted to complete case analysis did not materially affect any results (data not shown).
* Multivariable logistic regression after adjusting for age, sex, MS type, disability level, and whether participant was experiencing ongoing symptoms from a relapse in the previous 30 days.

be useful if this study confirms the findings here.

6. Conclusion

We investigated whether a more restricted DMD allocation in MS negatively impacted on clinical course, fatigue and quality of life. We found the expected differences in disability, but no differences were seen in fatigue, depression, or quality of life. Thus, in this setting, there appears to be no deleterious impact of more restrictive treatment allocation on quality of life in MS.

Author contributions

Drafting, analysis, and interpretation (AZZP); supervision of statistical analyses (SSJ), and editing of final manuscript (SSJ); Project inception, data collection, supervision of drafting, statistics, interpretation, and editing of final manuscript (GJ, TW, SSJ). All authors have reviewed and contributed to the draft manuscript and approve it for submission.

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Table 5
Univariable and adjusted OR of characteristics of depression risk (PHQ-2 > 2).

	Positive depression screen (PHQ-2 ≥ 3)	Univariable OR (95% CI)	Adjusted OR * (95% CI)
DMD use*			
None	30/264 (11.4%)	1.00 [Reference]	1.00 [Reference]
First-generation	55/386 (14.3%)	1.30 (0.81, 2.09) $p = 0.29$	0.99 (0.59, 1.68) $p = 0.98$
Second-generation	27/122 (22.1%)	**2.22 (1.25, 3.93)** $p = \mathbf{0.006}$	1.41 (0.73, 2.72) $p = 0.31$
Country			
Australia	92/578 (15.9%)	1.00 [Reference]	1.00 [Reference]
New Zealand	20/194 (10.3%)	0.61 (0.36, 1.02) $p = 0.057$	**0.54 (0.31, 0.95)** $\boldsymbol{p = 0.032}$

Results in boldface denote statistical significance ($p < 0.05$).
Multivariable models consisted of 707 observations (complete case analysis).
Note: Univariable results restricted to complete case analysis did not materially affect any results (data not shown).
* Multivariable logistic regression after adjusting for age, sex, MS type, disability level, clinically significant fatigue, and use of antidepressant medication.

Table 6
Univariable and adjusted OR of characteristics of physical and mental health-related quality of life

	Physical health-related QoL Univariable β (95% CI)	Adjusted β * (95% CI)	Mental health-related QoL Univariable β (95% CI)	Adjusted β * (95% CI)
DMD use*				
None	0.00 [Reference]	0.00 [Reference]	0.00 [Reference]	0.00 [Reference]
First-generation	−1.48 (−4.98, 2.01)	−2.08 (−4.80, 0.64)	−1.71 (−4.85, 1.44)	−0.17 (−3.31, 2.97)
	$p = 0.41$	$p = 0.13$	$p = 0.29$	$p = 0.91$
Second-generation	**−6.67 (−11.40, −1.95)**	**−4.12 (−7.75, −0.49)**	**−5.83 (−10.08, −1.57)**	−3.05 (−7.19, 1.09)
	$\mathbf{p = 0.006}$	$\mathbf{p = 0.026}$	$\mathbf{p = 0.007}$	$p = 0.15$
Country				
Australia	0.00 [Reference]	0.00 [Reference]	0.00 [Reference]	0.00 [Reference]
New Zealand	0.61 (−3.05, 4.26)	**3.83 (1.24, 6.41)**	1.73 (−1.54, 4.99)	2.33 (−0.66, 5.32)
	$p = 0.75$	$\mathbf{p = 0.004}$	$p = 0.30$	$p = 0.13$

Results in boldface denote statistical significance ($p < 0.05$).
Physical quality of life multivariable model consisted of 587 observations; mental quality of life multivariable model consisted of 680 observations (complete case analysis).
Note: Univariable results restricted to complete case analysis did not materially affect any results (data not shown).
* Multivariable linear regression after adjusting for age, sex, MS type, disability level, clinically significant fatigue, and whether participant was experiencing ongoing symptoms from a relapse in the previous 30 days.

Table 7
Differences in DMD-outcome associations between Australia and New Zealand

Relapses in the preceding year[a]	DMD Use	Australia aOR (95% CI)	NZ	Test for difference
(1 relapse vs no relapse)	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	0.59 (0.34, 1.04)	0.56 (0.24, 1.30)	$p = 0.91$
	Second-generation	0.74 (0.38, 1.42)	0.33 (0.03, 3.43)	$p = 0.52$
(2 or more relapses vs no relapse)	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	0.77 (0.43, 1.40)	1.00 (0.46, 2.15)	$p = 0.59$
	Second-generation	0.78 (0.39, 1.59)	0.43 (0.04, 4.50)	$p = 0.62$
Disability[b]				
(Gait/cane disability vs normal/mild disability)	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	1.45 (0.80, 2.65)	**3.93 (1.81, 8.55)**	$\mathbf{p = 0.036}$
	Second-generation	**3.35 (1.66, 6.79)**	7.27 (0.87, 61.05)	$p = 0.49$
(Major mobility support vs normal/mild disability)	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	1.03 (0.36, 2.92)	3.64 (0.89, 14.83)	$p = 0.14$
	Second-generation	**5.17 (1.67, 15.99)**	***	-
Clinically significant fatigue[c]	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	**1.87 (1.14, 3.07)**	1.19 (0.58, 2.44)	$p = 0.29$
	Second-generation	**1.89 (1.02, 3.52)**	***	-
Depression risk (PHQ-2)[d]				
Positive vs negative depression screen	None	1.00 [Reference]	1.00 [Reference]	
	First-generation	0.68 (0.37, 1.28)	1.48 (0.52, 4.17)	$p = 0.21$
	Second-generation	0.85 (0.41, 1.77)	9.18 (0.69, 122.14)	$p = 0.081$
		β (95% CI)		
Physical quality of life[e]	None	0.00 [Reference]	0.00 [Reference]	
	First-generation	−0.12 (−3.48, 3.24)	−3.05 (−7.85, 1.75)	$p = 0.31$
	Second-generation	−1.81 (−5.93, 2.30)	−6.15 (−21.89, 9.59)	$p = 0.60$
Mental quality of life[e]	None	0.00 [Reference]	0.00 [Reference]	
	First-generation	0.26 (−3.60, 4.13)	1.10 (−4.43, 6.63)	$p = 0.80$
	Second-generation	−1.52 (−6.21, 3.17)	−16.81 (−34.07, 0.46)	$p = 0.091$

Results in boldface denote statistical significance ($p < 0.05$).
*** Could not be quantitatively assessed due to small cell size.
[a] Adjusting for age, sex, and MS type.
[b] Adjusting for age, sex, MS type, and whether participant was experiencing ongoing symptoms from a relapse in the previous 30 days.
[c] Adjusting for age, sex, MS type, disability level, and whether participant was experiencing ongoing symptoms from a relapse in the .previous 30 days.
[d] Adjusting for age, sex, MS type, disability level, clinically significant fatigue, and use of antidepressant medication.
[e] Adjusting for age, sex, MS type, disability level, clinically significant fatigue, and whether participant was experiencing ongoing symptoms from a relapse in the previous 30 days.

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Conflict of interest statement

Aung Zaw Zaw Phyo, William Bevens, Tracey J. Weiland, Alysha M De Livera, Chelsea R. Brown, Emily O'Kearney, Steve Simpson, Jr.: No conflicts of interest to declare.

George A. Jelinek receives royalties for his books, Overcoming Multiple Sclerosis and Recovering from Multiple Sclerosis, and has received remuneration for conducting lifestyle educational workshops for people with MS.

Sandra L. Neate has received remuneration for conducting lifestyle educational workshops for people with MS.

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